A Mathematical Method for Calculating Lifespan

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Abstract

Over the next twenty years, the financial burden on the U.S. government to provide quality healthcare to its aging population is expected to rise to $4.2 trillion (U.S. Centers, 2006). One way the U.S. government could reduce the financial impact of this aging demographic is through funding research into the causes of aging such as telomeres. This work presents a method for calculating lifespan based on the rate of telomere shortening. By applying the Hayflick limit, it was possible to calculate the lifespan of an unknown organism by dividing the Hayflick limit (raised to the exponent of 2^{50}) with the square of the genomic library of a human. Then multiplying this number with the maximum lifespan (in seconds) of a human: thereby giving the rate of telomere shortening. To calculate the lifespan of an unknown organism it is first necessary to find the exponential Hayflick limit of that organism, and then divide it by the rate of telomere shortening: resulting in the predicted lifespan of the unknown organism. When applied to various organisms, such as a mouse, it was erroneous; however, further adjustments to the method corrected this mistake. Thus, the assumptions behind this method, according to the data, were essentially correct, and demonstrated a profound link between lifespan and the molecular timing mechanism that govern it. Applying this method for calculating lifespan and the rate of telomere shortening could lead to early detection of cancer, as well as the development of anti-aging drugs to extend lifespan.

Introduction

Because of the dramatic increase in the elderly population – expected to double by 2030 (U.S. Census Bureau, 2005) – scientists have now focused their attention to diseases prevalent within this aging demographic that, in the next twenty years, will require urgent medical treatment. The dilemma faced to an already overstretched healthcare system is the one reason for investigating the mechanisms that regulate aging – telomeres. Therefore, it is vital to establish telomeres' role in regulating aging and lifespan. Our understanding of cellular aging has greatly improved, since Leonard Hayflick showed that normal fibroblasts divide about fifty times before succumbing to senescence, overturning the notion of normal cell immortality proposed by Alexis Carrel (Fossel, 2004). Essentially, the Hayflick limit helps maintain cellular homeostasis by preventing the proliferation of cancerous cells. Investigators have discovered a major difference between normal cells and cancer cells that may account for the cancerous cells' ability to replicate indefinitely: Human cancer cells contain greater concentrations of telomerase, whereas normal cells generate low concentrations of this enzyme periodically (Weaver, 2008). Telomerase plays a vital role in maintaining telomere length namely through its actions of adding telomere repeats of TTAGGG to single stranded 3' overhangs resulting in a t-loop formation (de Lange, 2005). Forming a protective t-loop complex with shelterin enables telomeres to suppress DNA damage and prevent recombination at chromosome ends. However, disruption of this t-loop complex through telomere shortening or uncapping triggers cellular senescence that ultimately leads to cell death (Blackburn, 2000). Once a cell has reached, according to the Hayflick Limit, the permissible number of cell divisions apoptosis or programmed cell death is initiated. However, cancerous cells prevented apoptosis from happening. On the other hand, mutations in the RecQ family DNA helicase *wrn* gene are associated with the Werner syndrome (WS): a disease that causes accelerated aging and cancers in humans. Cells cultured from WS patients have reduced life spans. However, when WS fibroblasts are transfected with the human telomerase gene their life spans increased (Lee et al, 2004). Previous work suggests a telomerase-dependent pathway that affects cellular senescence, through the reduction in the number of mitotic divisions (Lee et al, 2004).

Most cells replicate according to a set number of mitotic divisions, that varies with different organisms, known as the Hayflick limit. With each mitotic division, the ends of chromosomes (a region known as telomeres) shorten, thus suggesting telomeres role as a timing mechanism for cellular senescence (Weaver, 2008). As a result, research on the biochemical and physiological effects of telomeres on aging is vital.

This work investigates the relationship between the Hayflick Limit and genomic library in determining longevity. The underlying premise is the observation that a cell has a finite number of divisions, the Hayflick limit, over a specific length of time. By calculating the rate in which a cell reaches the Hayflick limit will give the time it has left before dying, in other words, its lifespan. With each cellular division, the telomeres shorten and as telomeres are composed of nucleotides therefore one can logically assume that the genomic library will establish a cell's lifespan through cell division regulation. Therefore, it is logical to assume that the relationship between the Hayflick limit and telomeres is a factor affecting the inhibition of apoptosis, as is the case with cancer cells, and activation of apoptosis, as is the case with normal cells. This leads one to deduce a method for calculating lifespan based on this observation.

Materials

There was no physical experiment carried out in this paper. The mathematical equations used to predict lifespan were formulated from data that came from the scientific literature mentioned in the reference list of this paper. Observed lifespan data came from (Finch, 1990), genomic library size data came from (Weaver, 2008) and S phase duration data came from (Mitchison, 1971) and (Lee et al, 2004). The data obtained from these sources tested the validity of the method for calculating lifespan. A scientific calculator, a Casio fx-100s, computed the data. The organisms used to test this method were human, fruit fly, mouse, yeast, nematode, chicken, wheat, E. coli and dog.

Methods & Results

Hayflick limit influence on the method for calculating lifespan

Due to the variable nature of the Hayflick limit, with respect to tissue type and organism, it was necessary to apply the observed fibroblast Hayflick limit of fifty. Therefore, it is represented as 2^{50} where fifty is the number of mitotic divisions before succumbing to apoptosis. If we imagine a cell division cycle as the following equation ($n - 2^x$) where n is the total number of cellular divisions and 2^x represents the rate at which telomeres shorten – occurring in an exponential manner i.e. 2, 4, 6 .. 1.125×10^{15} (or 2^{50}). This number 1.125×10^{15} is referred to, in this paper, as the Longevity Number'. The rate at which telomeres shorten is derived from the Longevity Number' divided by the maximum lifespan of a human, say 120 years: lifespan must be converted into seconds. Therefore, the rate of telomere shortening will be as follows.

Equation 1.

$$\alpha = \frac{A}{B} y$$

α = rate of telomere shortening

A = Longevity No.

B = genomic library

y = lifespan in seconds

The rate of telomere shortening for humans is the following:

$(1.125 \times 10^{15} / 1.024 \times 10^{19}) \times (3{,}784{,}320{,}000 \text{ sec}) = 416{,}090$

By applying the known Longevity Number' i.e. (1.125×10^{15}) we can calculate the Longevity Coefficient' whereby an unknown Longevity Number' of another organism can be surmised.

Longevity coefficient = $1.125 \times 10^{15} / (1.024 \times 10^{19}) = 0.0001099$

Genomic Library^2 of human

Unknown Longevity No. = known genomic library^2 x 0.0001099 of organism to be studied

Lifespan of organism = Longevity No. of / 416,090 to be studied organism to be studied

Predicting the lifespan of *D. melanogaster* (fruit fly) requires calculating its Longevity Number, which is later divided by the rate of telomeres shortening as found in humans.

Therefore Longevity Number = genomic library^2 (3.24×10^{16}) x 0.0001099 of *D. melanogaster*

Therefore Longevity Number = 3.56×10^{12} of *D. melanogaster*

Calculated Lifespan = $3.56 \times 10^{12} / 416{,}090 = 8{,}561{,}634$ secs ≈ 99 days of *D. melanogaster*

However, when the mathematical method was applied to *Mus musculus*, in order to ascertain its lifespan, resulted in the following prediction:

Therefore Longevity Number = genomic library^2 (6.25×10^{18}) x 0.0001099 of *Mus musculus*

Therefore Longevity Number = 6.87×10^{14} of *Mus musculus*

Calculated Lifespan = $6.87 \times 10^{14} / 416{,}090 = 1.65 \times 10^{9}$ secs or 52 years of *Mus musculus*

The predicted lifespan of the *Mus musculus* (mouse) was 52 years, which contradicts the observed lifespan of *Mus musculus*. Therefore, if the lifespan of a mouse is 2 years or 63,072,000 seconds, then, by reapplying Equation 1 it was possible to recalculate the telomere shortening. Thus, the telomere shortening rate will be less than that of a human so the rate will be the following: $(6.87 \times 10^{14} / 6.25 \times 10^{18})$ x 63,072,000 secs = a telomere shortening rate of 6,932

By dividing the telomere shortening rate of the mouse (6,932) with that of a human (416,090) gave a Longevity coefficient of 0.0166

To calculate lifespan came from Equation 2:

Equation 2.

$$y = \frac{B\alpha}{A}$$

y = lifespan in seconds

B = genomic library

α = rate of telomere shortening

A = Longevity No.

(genomic library^2 of i.e. mouse x corrected telomere shortening rate /Longevity No.)

Therefore 6.25 x 10^{18} x 6,932/6.87 x 1014 = 63,071,961 secs or 1.99 years.

Knowing the average lifespan of *D. melanogaster* resulted in the following observation. Lifespan of fruit fly is approximately 40 days or 3,456,000 secs. Thus the telomere shortening rate will be: (3.56 x 10^{12}/3.24 x 10^{16}) x 3,456,000 secs = a telomere shortening rate of 379. Reapplying Equation 2 gave following fruit fly lifespan: 3.24x10^{16} x 379/3.56x 10^{12} = 3,455,969 secs or 39.9 days

Dividing the telomere shortening rate of the fruit fly (379) with that of a human (416,090) gave a Longevity coefficient of 0.000912. Therefore, the Longevity coefficient decreases in an ordered way such as 0.0166 to 0.000912. Thus, 0.0166 is used as a means to obtain the decreasing rate of telomere shortening. By multiplying this with 416,090 and with each declining rate value of 0.0166 it is reduced by a decimal place resulting in an approximate value of telomere shortening for various organisms.

0.0166 x 416,090 = 6,932

0.00166 x 416,090 = 693.2

0.000166 x 416,090 = 69.32

0.0000166 x 416,090 = 6.932

0.00000166 x 416,090 = 0.6932

Lifespan for *Mus musculus* = 6.25 x 10^{18} x 6,932/6.87 x 10^{14} = 63,064,046 secs or 1.99 years

Lifespan for *D. melanogaster* = 3.24 x10^{16} x 693.2/3.56 x10^{12} = 6,308,898 secs or 73 days

Lifespan for *Nematode* = 9.4 x 10^{15} x 69.32/1.033 x 10^{12} = 630,791 secs or 7.3 days

Lifespan for *budding yeast* = 3.24 x 10^{14} x 6.932/3.56 x 10^{10} = 63,088 secs or 17.52 hours

Lifespan for *E. coli* = 2.116 x 10^{13} x 0.6932/2.32x10^{9} = 6,322 secs or 1.75 hours

Organisms such as dogs that have approximately the same genomic size as a mouse, but a longer lifespan than a mouse, would simply be: 0.166 x 416,090 = 69,320

Thus, reapplying Equation 2 will give the lifespan for a dog:

= 5.76 x 10^{18} x 69,320 /6.33 x10^{14}

= 630,779,146 secs or 20 years

Anecdotal reports suggest the lifespan of a chicken to be 15 years (Finch, 1990). If this is the case, then calculating its telomere shortening will be: 69,320 (dog telomere shortening) – 13,864 (twice the mouse telomere shortening) = 55,456

Thus, reapplying equation 2 will give the lifespan for a chicken:

= 1.1025 x 10^{18} x 55,456/1.21 x 10^{14}

= 505,291,239 secs or 16 years

The lifespan for plants can vary considerably, some are annuals other are perennial and yet others have both life histories depending on the conditions (Finch, 1990). For instance, peas and wheat in particular have larger genomes than humans do, thus one can assume that their lifespan will not be in the order of 120 years. As wheat is an annual, its telomere shortening will be half that of the mouse or 3,466.Thus, reapplying Equation 2 will give the lifespan for wheat:

$= 2.56 \times 10^{20} \times 3{,}466 / 2.81 \times 10^{16}$

= 31,576,370 sec or 1.00 year

Table 1 Summary of predicted lifespan versus observed lifespan results.

Organism	***Genome[2]***	***Longevity No.***	***Telomere shortening approximate***	***Telomere Shortening adjusted***	***Predicted Lifespan ****	***Observed lifespan***
Mus musculus	6.25×10^{18}	6.87×10^{14}	6,932	8,130	2.34 years	2-3 years
D. melanogaster	3.24×10^{16}	3.56×10^{12}	693	320	33.7 days	30-40 days
Nematode	9.4×10^{15}	1.033×10^{12}	69.3	115	12.11 days	11-15 days
Budding yeast	3.24×10^{14}	3.56×10^{10}	6.93	130	13.69 days	14 days
E. coli	2.15×10^{13}	2.36×10^{9}	0.693	0.693	1.75 hours	?
Chicken	1.1025×10^{18}	1.21×10^{14}	69,320	52,000	15 years	15 years
Wheat	2.56×10^{20}	2.81×10^{16}	6,932	3,466	1 year	1 year
Dog	5.76×10^{18}	6.33×10^{14}	69,320	46,790	13.5 years	12-15 years

*Predicted Lifespan calculated using adjusted Telomere shortening rate and reapplying Equation 2.

S phase influence on the method for calculating lifespan

Mitotic division is characterized by the separation of a cell into two daughter cells. In higher eukaryotes, like humans, it involves division of the nucleus and the cytoplasm. In most proliferating cells, mitotic division proceeds in an orderly fashion taking approximately 10-20 hours depending on cell type and development state. For the duration of mitotic division, the cell divides according to pre-programmed growth phases: the interphase, which consists of the G1, S and G2; and then the mitotic

(M) phase (Lodish, 2004). During S phase the combined genome of both daughter cells would equate to the square of the genomic library of that particular organism, i.e. for humans that would be 1.024 x 10^{19}. The genomic library is the entire DNA sequence of the organism where it is tightly coiled into chromosomes. During mitosis, the DNA sequence is unwound from the chromosome before being replicated twice and included into the newly formed daughter cells. Apoptosis induced by telomere shortening is coupled to S phase. However, telomerase deficiency results in direct activation of apoptosis bypassing mitosis (Rajaraman et al, 2007). Therefore, one can logically assume that the S phase duration is a means in testing the validity of the method for calculating lifespan based on telomere shortening influenced by telomerase sensitivity. To calculate S phase duration came from Equation 3.

S phase duration = $\sqrt{\frac{B\ \alpha}{A}}$

B = genomic library

α = rate of telomere shortening

A = Longevity No.

Equation 3

S phase duration for Human = $(1.024 \times 10^{19} \times 416{,}090 / 1.125 \times 10^{15})^{1/2}$ = 61,541 secs or 17 hours

S phase duration for Mouse = $(6.25 \times 10^{18} \times 8{,}130 / 6.87 \times 10^{14})^{1/2}$ = 8,600 secs or 2.38 hours

S phase duration for Fruit Fly = $(3.24 \times 10^{16} \times 320 / 3.56 \times 10^{12})^{1/2}$ = 1,706 secs or 28.44 mins

S phase duration for Nematode = (9.4 x 1015/sup] x 115/1.033 x 1012)1/2 = 1,022 sec or 17 min

S phase duration for budding Yeast = (3.24 x 1014 x 130 /3.56 x 1010)1/2= 1,087 sec or 18.12 mins

S phase duration for E. coli = (2.15 x 1013 x 0.6593 /2.36 x 109)1/2 = 77 sec or 1.29 mins

Table 2 Summary of predicted S phase versus observed S phase results.

Organism	***Predicted S phase duration***	***Observed S phase duration***
Human	17 hours	≈ 6 hours
Mouse	2.38 hours	6 hours
Yeast	18 minutes	≈ 10 minutes
Nematode	17 minutes	16 minutes

Discussion

The predicted lifespan based on approximate telomere shortening was found to be 1.99 years for a mouse, 73 days for a fruit fly and 7.3 days for a nematode; compared with the observed lifespan of 2-3 years for a mouse, 30-40 days for a fruit fly and 11.5 – 15 days for a nematode (Finch, 1990). However, when the approximate telomere shortening rate was adjusted the predicted lifespan matched that of the observed lifespan, as in the case of the chicken and wheat species. Table 1 gives an overview of the results and shows that by adjusting telomere shortening rate for all organisms produced similar lifespan to those observed. Comparing the actual lifespan with that of those predicted showed that the basic notions regarding this mathematical method are primarily correct. Since microorganisms such as yeast and E. coli are asexual, it is difficult to ascertain accurately their lifespan. Given a plentiful supply of nutrients and the right temperature for cellular division, microorganisms will divide indefinitely. Such progenitor cells will in time die, but this is dependent on the generation time of the organism. For instance, by adjusting the telomere shortening rate of *yeast* from 6.932 to 138, and reapplying Equation 2: gave a lifespan of 14.5 days, which matches the literature value of 14.6 days (Finch, 1990).

As cell cycles vary considerably between organisms and tissue type, calculating the S phase duration is difficult. Therefore, the predicted S phase duration times will not exactly match the observed times. Bearing this in mind, the predicted S phase duration for a mouse was 2.38 hours, for a budding yeast 18.12 minutes and for a nematode 17 minutes; compared with the observed S phase of 6 hours for mouse L cells, ≈ 10 minutes for fission yeast (Mitchison, 1971) and 16.1 minutes for wild type nematodes (Lee et al, 2004). Although the predicted S phase duration times did not exactly match, they do tend to fall within an acceptable margin of error. Comparing the observed S phase with that of the predicted ones showed that the basic notions regarding this mathematical method are primarily correct; however, the Human S phase seems too long because the observed time, according to Mitchison, is similar to that of a mouse ≈ 6 hours.

With further refinements, this method of calculating lifespan will result in accurate predictions, and the assumption behind this method clearly demonstrates telomere's possible involvement in molecular timing. Further investigations regarding telomere's possible involvement in cellular senescence and cancer could lead to new therapies to treat these disorders. Monitoring the rate at which telomeres shorten could result in the detection of cancer cells due to their ability to inhibit telomere shortening. On the other hand, treatment with anti-aging drugs that inhibit the degradation of telomeres could result in the extension of human lifespan. However, as such drugs could lead to the proliferation of cancer cells, it is vital to establish the safety of such drugs. This mathematical method could monitor the level of inhibition of telomere shortening, and thereby establish a therapeutic dose for anti-aging drug, reducing the likelihood of cancer.

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